UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
|---|---|---|---|---|
| 09/719,219 | 03/28/2001 | Jean-Michel Bernardon | 016800-425 | 7072 |

21839 7590 05/05/2004

BURNS DOANE SWECKER & MATHIS L L P
POST OFFICE BOX 1404
ALEXANDRIA, VA 22313-1404

| EXAMINER | |
|---|---|
| ROBINSON, BINTA M | |

| ART UNIT | PAPER NUMBER |
|---|---|
| 1625 | |

DATE MAILED: 05/05/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 09/719,219 | BERNARDON ET AL. | |
| | Examiner | Art Unit | |
| | Binta M. Robinson | 1625 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1-13 and 15-20* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-13 and 15-20* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

**Detailed Action**

Claims 1-13, 15-20 are pending in the application.

The elected group I invention at paper no. 7, drawn to claims 1-13, 15-20 to the compound of formula I in claim 1 where Ar is pyridyl, R1 is COOH, R2 and R3 come together to form a saturated benzo moiety where the ring carbons are not optionally replaced with oxygen or sulphur atoms, R4 is lower alkyl radical, a method of treating, and a composition, has been examined below and is made FINAL. The unelected portions of claims 1-13 and 15-20 are withdrawn from consideration and examination. If the applicant does not narrow the claims to the elected subject matter, then 102 (b) rejections will be made over references such as Ca 85:192503.

**(Old Rejections)**

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1 and 10 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A. In claim 1, the phrase "amino acid residue" in line 9, page 5 of the amendment filed 1/24/04 is ambiguous. It is not clear what derivatives or residues of the amino acids are being claimed?

B. The phrase, "amino acid residues are selected from the group consisting of residues derived from lysine, glycine, and aspartic acid" in claim 10, line 1-2, page 6 of amendment 10/B. is indefinite. The phrase is indefinite because it is unclear as to

what moieties are actually being claimed, since only a residue of the claimed amino acids are being claimed, and it is unclear as to what residues are being claimed. The specification on page 6 only explains the phrase "amino acid residue" as being for example, a moiety from one to 20 amino acids of L or D configuration which constitutes mammalian proteins. If the applicant can point out where in the specification, amino acid residues are delineated by actual specific chemical moieties, then this language would be a better substitute than "amino acid residues". However, it does not appear that the applicant has clearly defined in the specification what amino acid residues are in terms of specific chemical moieties.

**(Modified Rejection)**

1. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 1 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. There is insufficient description of what geometric isomers of the compound of formula I is being claimed. In the absence of how to synthesize these geometric isomers, there is no umbrella coverage springing forth from the claimed

compound of formula I and the few examples of geometric isomers depicted in the specification.

Claims 1-13 and 15-20 are rejected under 35 U.S.C. 112, first paragraph, because the specification, does not provide enablement for the compounds of formula I where R2 and R3 taken together with the adjacent aromatic ring, forms 5 or 6 membered saturated rings optionally substituted with methyl groups and/or optionally interrupted with an oxygen or sulfur atom, other than tetrahydronapthyl. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims. The claims as recited are broader than the scope of enablement. The specification lacks direction or guidance for placing all of the alleged products in the possession of the public without inviting more than routine experimentation. The applicant is referred to ***In re Wands***, 858 f.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988) which includes the incorporation of the 8 factors recited in ***Ex parte*** Foreman 230 USPQ 546 (Bd. Of App. And Inter 1986).

Claim 15 is rejected under 35 U.S.C. 112, first paragraph, because the specification, does not reasonably provide enablement for the method of treating any dermatological complaint associated with keratinization disorder which has a bearing on differentiation and on proliferation; for treating any type of keratinization disorder; for treating any other dermatological complaint associated with a keratinization disorder with an inflammatory and/or immunoallergic component; for treating any inflammatory complaints which have no keratinization disorder; for treating any dermal or epidermal

proliferations, whether benign or malignant and whether they are of viral origin or otherwise, for any opthalmological disorder, for repairing or combating any ageing of the skin, for reducing any actinic keratoses and pigmentations, or for treating and preventing any pathology associated with chronological or actinic ageing; for preventing or curing any stigmata of epidermal and/or dermal atrophy induced by local or systemic corticosteroids, or for treating any form of cutaneous atrophy, for preventing or treating any cicatrisation disorder or for preventing or repairing stretch marks or for promoting cicatrisation, or for combating any disorder of sebaceous functioning hyperseborroea of acne or for treating any or preventing any cancerous or precancerous states, or for treating any inflammatory complaints, or any of the other diseases claimed in claim 15. Nor does the specification provide enablement for the use of these compounds as body or hair hygiene. It is not established in the art for any drug to prevent any disease, particularly cancer or precancerous states, alopecia, cicatrisation disorders, stretch marks. An agonist of a receptor site and an antagonist of a receptor site without a preliminary screening test gives no clear indication that the compounds would have the alleged properties. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims. The claims as recited are broader than the scope of enablement.

In *In re Wands*, 8 USPQ2d 1400 (1988), factors to be considered in determining whether a disclosure meets the enablement requirement of 35 U.S.C. § 112, first paragraph, have been described. They are:

1. the nature of the invention,
2. the state of the prior art,
3. the predictability or lack thereof in the art,
4. the amount of direction or guidance present,
5. the presence or absence of working examples,
6. the breadth of the claims,
7. the quantity of experimentation needed, and
8. the level of the skill in the art.

**The Nature of the Invention**

The nature of the invention is that these compounds are useful as cosmetic compositions for body and hair hygiene.

**State of the Prior Art**

Selenium is known in the art as a naturally occurring antioxidant, which is capable of neutralizing free radicals that might otherwise damage genetic material of cells and possibly lead to cancer. (See Oncology, Vol. 15, No. 11, November 2001, See Reference U). Nakanishi et. al. Discloses the diaryl selinium compounds involving naphthalene and phenyl (See Reference V). Diaz discloses the synthesis of diarylselenium-containing compounds that can activate the retinoic acid receptor, RXR and tetrahydronapthyl seleno compounds. (See Reference W). Diaz found new RXR antagonists among these diarylselenium –containing compounds, and found that compound 29 was 10 times more potent as an RXR agonist than its sulfur analogue, page 1708. Diaz discloses that selenium containing retinoids have exerted profound effects on cell differentiation, proliferation, and that therefore, selenium retinoids have a high potential for the treatment of hyperproliferative disorders such as psoriasis or cancer. Diaz discloses that many of these disorders are mediated by the activation of

nuclear receptors, particularly retinoic acid receptors RAR and RXR located in the cell nucleus. (See page 1706, of Diaz)

**The Lack of Predictability in the Art**

The instant claimed invention is highly unpredictable as discussed below:

It is noted that the pharmaceutical art is unpredictable, requiring each embodiment to be individually assessed for physiological activity. In re Fisher, 427 F.2d 833, 166 USPQ 18 (CCPA 1970) indicates that the more unpredictable an area is, the more specific enablement is necessary in order to satisfy the statute. In the instant case, the instant claimed invention is highly unpredictable since one skilled in the art would recognize that in regards to therapeutic effects of RXR-mediated diseases, whether the RXR was the compounds of claim 1 with agonist or antagonist activity would affect the possible treatment of any disease.

Hence, in the absence of a showing of correlation between all the diseases claimed and disclosed as capable of treatment by the compound of claim 1 and the activation of RXR, one of skill in the art is unable to fully predict possible results from the administration of the compound of claim 1 due to the unpredictability of the role of RXR, i.e. whether binding and activation would be beneficial for the treatment of the diseases.

The nature of pharmaceutical arts is that it involves screening *in vitro* and *in vivo* to determine which compounds exhibit the desired pharmacological activities. There is no absolute predictability even in view of the seemingly high level of skill in the art. The existence of these obstacles establishes that the contemporary knowledge in the art

would prevent one of ordinary skill in the art from accepting any therapeutic regimen on its face. Also, the level of predictability in the art is low because the applicant does not conduct any tests of these compounds for their effects as cosmetic compositions.

**The amount of direction or guidance present**

The direction present in the instant specification is that the compounds of claim 1 are agonists or antagonists of RXR which helps in the treatment for the diseases disclosed in the specification and claimed in claim 15. However, the specification is silent and fails to provide guidance as to whether the diseases listed as RXR-mediated diseases would benefit from the agonist or antagonistic activity of the instant compounds. The specification provides no experimental data on the agonist or antagonistic activity of these compounds on RXR or the effects of these compounds on the specific diseases claimed.

**The presence or absence of working examples**

The specification does not provide any experimental data on the on the agonist or antagonistic activity of these compounds on RXR or the effects of these compounds on the specific diseases claimed. Also, the compounds which are disclosed in the specification as well as those compounds that are claimed, have no pharmacological data regarding the treatment of any other disease. Also, the specification fails to provide working examples as to how the listed diseases can be treated by having the instant compounds serve as agonists or antagonists to RXR. In terms of the sixth Wands factor, the amount of direction provided by the inventor is poor, because the applicant does not synthesize compounds where R2 and R3 come together to form any

ring with the phenyl ring to which it is bound, other than tetrahydronapthyl. The applicant also does not synthesize compounds for example, where two nitro groups exist in the ortho position. The applicant also does not test the effects of these compounds as cosmetics.

**Breadth of the Claims**

The breadth of the claims is that the compound of claim 1 can treat the diseases claimed in claim 15 or can be used in a method for body or hair hygiene as claimed in claim 20, without regards as to the affect of RXR on the stated diseases.

In terms of the breadth of the claims, for R2 and R3 taken together with the adjacent aromatic ring, and aryl or aralkyl optionally substituted as claimed encompass a much wider Markush grouping of radicals than those radicals synthesized and tested.

**The quantity of experimentation needed**

The quantity of experimentation needed is undue experimentation. One of skill in the art would need to determine what listed diseases would be benefited by the activation of RXR and would furthermore then have to determine whether the claimed compounds would provide treatment of the claimed diseases by activating RXR. .

**The level of the skill in the art**

The level of skill in the art is high. However, due to the unpredictability in the pharmaceutical art, it is noted that each embodiment of the invention is required to be individually assessed for physiological activity by in vitro and in vivo screening to determine which compounds exhibit the desired pharmacological activity and which diseases would benefit from this activity.

Thus, the specification fails to provide sufficient support of the broad use of the compound of the claim 1 for the treatment of the various disease states claimed in claim 15 and for the use of the compound for body or hair hygiene in claim 20. As a result necessitating one of skill to perform an exhaustive search for which disclosed and claimed can be treated by the compound of claim 1 in order to practice the claimed invention.

Genentech Inc. v. Novo Nordisk A/S (CA FC) 42 USPQ2d 1001 , states that " a patent is not a hunting license. It is not a reward for search , but compensation for its successful conclusion" and "[p]atent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable".

Therefore, in view of the Wands factors and In re Fisher (CCPA 1970) discussed above, to practice the claimed invention herein, a person of skill in the art would have to engage in undue experimentation to test which claimed diseases can be treated by the compound encompassed in the instant claims, with no assurance of success.

**Quantity of Experimentation**

In terms of the 8th Wands factors, undue experimentation would be required to make or use the invention based on the content of the disclosure due to the breadth of the claims, the level of predictability in the art of the invention, and the poor amount of direction provided by the inventor. Taking the above factors into consideration, it is not seen where the instant claim is enabled by the instant application.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A. In claim 1, line 17, page 5, the phrase "and the optical and geometric isomers of the said compounds of formula (I)" is ambiguous. Claim 1 is a compound claim claiming one compound, yet it is also claiming optical and geometric isomers. A compound claim by definition can only contain one compound, not more than one compound. It is suggested that the phrase be amended to -- or the optical or geometric isomer of the said compound of formula (I)--.

B. Claim 4 recites the limitation "it being possible for the monohydroxyalkyl radical to be protected in the form of acetyl or tertbutyldimethylsilyl" in line 3, page 6. There is insufficient antecedent basis for this limitation in the claim.

C. Claim 5 recites the limitation "it being possible for the hydroxy radical to be protected in the form of acetyl or tertbutyldimethylsilyls" in line 3, page 6.

D. Claim 11 recites the limitation "heterocyclic radicals selected from the group consisting of piperidino, morpholino, pyrrolidino and piperazino" in lines 2-3, page 8.

E. Claim 12 recites in line 2, page 8, the phrase "alone or as mixtures" is ambiguous because claim 12 is a compound claim, yet mixtures are being claimed as well. A compound claim by definition can only consist of one compound. A mixture consists of 2 or more compounds. Is the applicant claiming a compound or a mixture?

F. In claim 18, page 13, line 1, the "]" is ambiguous. Brackets usually denote that subject matter is being deleted from the claims. The applicant only has one bracket and not two. What is the purpose of "]" in the claim?

G. In claim 15, line 7, page 12, the phrase "or otherwise" is indefinite and ambiguous because it is not clear what origin of the proliferations is being depicted.

H. In claim 15, lines 8-9, the phrase "certain ophthalmological disorders" is ambiguous? What certain ophthalmological disorders is the applicant claiming?

I. Regarding claim 15, the phrase "such as" renders the claim indefinite because it is unclear whether the limitations following the phrase are part of the claimed invention. See MPEP § 2173.05(d).

J. Claims 16-19 are indefinite, because there is no reference to a pharmaceutically acceptable carrier that is inert.

G. In claim 1, line 8, page 2, and everywhere else throughout claim 1, the phrase "meanings given below" is indefinite. It is not clear if the applicant is referring to the meanings given below in claim 1 or in later claims.

H. In claim 15, page 12, the phrase, "dermatological complaints" is ambiguous. Is the applicant referring to dermatological diseases and if so which ones?

I. In claim 15, page 12, the phrase "preventing" --- "cicatrisation or for preventing stretchmarks" is ambiguous. The applicant is claiming all future uses for this drug that have not been established in the art.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Binta M. Robinson whose telephone number is (571) 272-0692. The examiner can normally be reached on M-F (9:30-6:00).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph McKane can be reached on 571-272-0699.

A facsimile center has been established. The hours of operation are Monday through Friday, 8:45 AM to 4:45 PM. The telecopier numbers for accessing the facsimile machine are (703)308-4242, (703)305-3592, and (703)305-3014.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (571)-272-1600.

BMR
May 3, 2004

JOSEPH K. McKANE
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600